Remarks

In the first paragraph on page 2 of the Action, the Examiner maintains the rejection of claims 16 and 18 (and, by implication, dependent claims 19-22) solely because the phrase "one of its variants or mutants" is vague and indefinite and not supported by the specification. On the contrary, Applicants respectfully submit that these terms, as well as how to obtain such mutants and variants, are adequately supported by the detailed discussion in the disclosure at pages 12 and 13 of the specification. In this connection, the Examiner's attention is directed to the annotated search results attached hereto as Exhibit "A" which documents a number of instances of recently issued U.S. patents that contain these terms in their claims and whose specifications contain no more supportive disclosure therefor (and often less) than that of the present application. Further, the process for obtaining such mutants and variants discussed on pages 12 and 13 of the present application produces only those that can be used to produce compounds of formula (I). Accordingly, this rejection is clearly untenable. It should be reconsidered and withdrawn.

Further, contrary to the Examiner's assertion with respect to claims 20-21, as noted in the first paragraph of the Remarks in that response, these claims were indeed amended in the response filed December 8, 2004 in accordance with the Examiner's suggestion in the Office Action of September 22, 2004, in the first complete paragraph on page 3 thereof, by deleting the recitation 'and/or prophylaxis' from the first line of claim 20. Therefore, claims 20 and 21 are indeed allowable, and their rejection should be withdrawn.

Finally, the rejection of claim 23 under 35 U.S.C. 102 discussed on pages 3 and 4 of the Action is respectfully traversed. As evidenced by the a copy of a letter dated 04-07-2005 from Dr Vera Weihs of the depository in question, DSMZ, to Dr. Frank Sieber of Aventis Pharma Deutschland GmbH, attached hereto as Exhibit "B," contrary to the assumption underlying the rejection - i.e. that deposit of the microorganism under the Budapest Treaty, as is the case for DSM14865, at the depository, DSMZ, placed it in the public domain - even the fact of the deposit was kept secret and out of the public domain until publication of the priority document from which priority is claimed in the present

application, all in accordance with the rules and regulations of the Budapest Treaty. See, particularly, the first paragraph on page 2 of the attached letter (Exhibit "B"). Accordingly, the rejection for lack of novelty based on applicants' own deposit of the microorganism in accordance with the Budapest Convention is untenable and should be withdrawn.

Conclusions

In view of the foregoing, it is submitted that all of the claims, as previously amended, are now in condition for Allowance. Prompt action to that effect is earnestly solicited.

Respectfully submitted,

Irving Newman, Reg. No. 22,638
Attorney/Agent for Applicant

Aventis Pharmaceuticals Inc.
Patent Department
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (908) 231-2785
Telefax (908) 231-2626

Aventis Docket No. DEAV2002/0046US NP

EXHIBIT "A"

Search in USPTO database for granted patents:

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aclm/mutant and exp/(tsang or oh)

relevant hits e.g. (all Primary Examiner = Tsang)

US 5,849,724*
US 5,885,959*

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aclm/(actinomycetales and mutant)

relevant hits

US 4,075,061
US 4,164,447

---

aclm/(variant and mutant) = 189 hits

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aclm/(microorganism and variant and mutant) = 33 hits, e.g.

US 5,919,671* (a BMS patent)
US 6,794,408* (= ex-Aventis internal number 2002/0005)

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* discussed in detail below

US 5,885,959

WE CLAIM:

1. A cyclic peptide compound selected from the group consisting of CJ-15,208; CJ-15,208-1; CJ-15,208-2 and CJ-15,208-3, wherein

(a) said CJ-15,208 has the following chemical formula (I): ##STR4## (b) said CJ-15,208-1 has the characteristic FAB mass spectrum with m/z 617 (M+H).sup.+, the UV spectrum with UV max at 210 and 280 nm, the .sup.1 H NMR spectrum shown in FIG. 2, and a retention time of 12.1 min on HPLC using a YMC Pack ODS column (6.0.times.150 mm) and eluting with methanol-water (60:40) at a flow rate of 0.8 ml/min at 42.degree. C.;

(c) said CJ-15,208-2 has the characteristic FAB mass spectrum with m/z 678 (M+H).sup.+ ; the UV spectrum with UV max at 210 and 280 nm; the .sup.1 H NMR spectrum shown in FIG. 3; and a retention time of 14.8 min on HPLC using a YMC Pack ODS column (6.0.times.150 mm) and eluting with methanol-water (60:40) at a flow rate of 0.8 ml/min at 42.degree. C.; and

(d) said CJ-15,208-3 has the characteristic FAB mass spectrum with m/z 539 (M+H).sup.+ ; the UV spectrum with UV max at 210 nm; the .sup.1 H NMR spectrum shown in FIG. 4; and a retention time of 17.8 min on HPLC using a YMC Pack ODS column (6.0.times.150 mm) and eluting with methanol-water (60:40) at a flow rate of 0.8 ml/min at 42.degree. C.

2. A process for producing cyclic peptide compounds according to claim 1, which comprises cultivating a microorganism Ctenomyces serratus FERM BP-5731, or a ***mutant*** or recombinant form thereof, and then isolating cyclic peptide compounds from the fermentation broth.

[...]

DESCRIPTION

In this invention, a mutant or recombinant form of FERM BP-5731 having the ability to produce the cyclic peptide compounds can be also used. The mutant or recombinant form may be obtained by spontaneous mutation, artificial mutation with ultraviolet radiation, or treatment with mutagen such as N-methyl-N'-nitro-N-nitrosoguanidine or ethyl methanesulfonate, or a cell technology method such as cell fusion, gene manipulation or the like, according to well-known methods.

According to the present invention, the cyclic peptide compounds may be produced by aerobic fermentation of FERM BP-5731, or a mutant or recombinant form thereof, under conditions similar to those generally employed to produce bioactive compounds by fermentation.

FERM BP-5731, or a mutant or recombinant form thereof, is usually fermented on solid medium with an insoluble material and aqueous nutrient media. The amount of the insoluble material may be in the range of 10 to 50% (w/v). Suitable insoluble materials useful for fermentation include sand, cracked stone, wood chip and whole broken grains, such as wheat bran, oatmeal, cracked corn, millet, etc. In this invention, cultivation of FERM BP-5731 to

produce the novel cyclic peptide compounds was preferably carried out using such insoluble materials and aqueous nutrient media at a temperature of 20.degree. to 35.degree. C. for 3 to 20 days. The pH of the medium may be adjusted in the range from 4.0 to 9.0, preferably from 5.0 to 7.5.

Example One

Fermentation of Ctenomyces serratus (FERM BP-5731)

[no example for mutant]

US 5,849,724

WE CLAIM:

1. A compound of the general formula I ##STR6## in which: R.sub.1 represents a C.sub.1 to C.sub.5 alkoxy group, an aldehyde group, a carboxyl group, a C.sub.1 to C.sub.5 alkyl ester or a (C.sub.1 to C.sub.5 alkyl)hydroxyl group,

R.sub.2 represents a hydrogen atom or a C.sub.1 to C.sub.4, linear or branched, lower alkyl group, and

R.sub.3 represents a C.sub.1 to C.sub.4 alkyl group, a hydroxyl group or a C.sub.1 to C.sub.4 alkoxy group,

or salt thereof.

2. A pharmaceutical composition comprising a pharmaceutically sufficient amount of the compound according to claim 1, or a slat thereof, or physiologically active pharmaceutically acceptable adjuvants.

3. A method for treating a mammal subject to having normal cells therein transformed into cancerous cells by administering to the mammal a farnesyl transferase inhibitory amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

4. A process for preparing the compound according to claim 1 comprising culturing Chrysosporium strain No. CBS 123.95, or ***mutant*** thereof, or derivative thereof, in a culture medium, and recovering by extraction from the culture medium the compound.

[...]

12. Chrysosporium strain No. CBS 123.95 or ***mutant*** thereof or derivative thereof.

DESCRIPTION

For the purpose of the present invention, derivative or mutant is understood to mean any strain obtained from the strain Chrysaosporium CBS 123.95 and capable of being used for the production of compounds according to the invention and more particularly exhibiting inhibitory properties towards the protein farnesyl transferase. In particular, such derivatives or mutants may be obtained by genetic modifications (alteration at the level of the DNA) or biochemical modifications. To this effect, various mutagenesis tools may be used, such as for example nonspecific tools:

physical agents (X-rays, ultraviolet rays and the like) or

chemical agents (alkylating or bialkylating agents, intercalating agents and the like), or specific tools such as DNA-directed mutational insertion systems (transposons, retrotransposons, integrative plasmids and the like).

The fermentation by this strain on a suitable culture medium and subsequent extraction of the corresponding fermentation broth makes it possible to isolate compounds which, although

having an original structure compared with conventional farnesyl transferase inhibitors, unexpectedly prove to be advantageous in this respect.

The present invention also relates to compounds capable of being obtained by fermentation by the Chrysosporium strain CBS 123.95 or one of its mutants via the extraction of a corresponding fermentation broth.

Another subject of the present invention relates to a process for the production of active metabolites according to which the Chrysosporium strain CBS 123.95 or one of its derivatives or mutants is cultured and at least one active metabolite is recovered.

[this is similar to what is said on page 12 of our application]

US 5,919,671

WE CLAIM:

1. A process for the preparation of BMS-199687 having the formula ##STR2## which comprises cultivating a BMS-199687-producing strain of Actinomadura ferruginea in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen under submerged aerobic conditions until a substantial amount of BMS-199687 is produced by said organism in such culture medium and then recovering said BMS-199687 from the culture medium.

2. The process according to claim 1 wherein the BMS-199687-producing strain is Actinomadura ferruginea strain WC57581 (ATCC-55733) or a ***variant*** or ***mutant*** thereof.

3. A biologically pure culture of the ***microorganism*** Actinomadura ferruginea strain WC57581 (ATCC-55733) which is capable of producing the antibiotic BMS-199687 of the formula ##STR3## in a recoverable quantity upon cultivation in a culture medium containing assimilable sources of carbon and nitrogen under submerged aerobic conditions.

DESCRIPTION

As in the case with other microorganisms, the characteristics of the new producing culture of the present invention, Actinomadura ferruginea ATCC-55733, are subject to variation. Recombinants, variants and mutants of the ATCC-55733 strain may be obtained by treatment with various known mutagens such as ultraviolet rays, X-rays, high frequency waves, phage exposure, radioactive rays and chemicals. Natural and induced variants, mutants and recombinants of Actinomadura ferruginea ATCC-55733 which retain the characteristic of producing BMS-199687 are intended to be encompassed by the present invention.

[no example for mutant or variant]

US 6,794,408

WHAT IS CLAIMED IS:

1. A compound of formula (I) ##STR7##

wherein:

R is H, or a group of the formula --(CH(OR.sup.2)).sub.5 --CH.sub.2 --OR.sup.2 ;

R.sup.1 and R.sup.2 independently are H, C.sub.1 -C.sub.6 -alkyl, C.sub.2 -C.sub.6 -alkenyl, C.sub.2 -C.sub.6 -alkenyl or C.sub.6-C.sub.10 -aryl, wherein said C.sub.1 -C.sub.6 -alkyl, C.sub.2 -C.sub.6 -alkenyl, C.sub.2 -C.sub.6 -alkynyl or C.sub.6 -C.sub.10 -aryl are optionally mono- or disubstituted by --OH, .dbd.O, --O--C.sub.1 -C.sub.6 -alkyl, --O--C.sub.2 -C.sub.6 -alkenyl, C.sub.6 -C.sub.10 -aryl, --NH--C.sub.1 --C.sub.6 -alkyl, --NH--C.sub.2 -C.sub.6 -alkenyl, --NH.sub.2 or halogen, wherein said --O--C.sub.1 --C.sub.6 -alkyl, --O--C.sub.2 -C.sub.6 -alkenyl, C.sub.6 -C.sub.10 aryl, --NH--C.sub.1 -C.sub.6 -alkyl and --NH--C.sub.2 -C.sub.6 -alkenyl substituents are optionally substituted by --CN, --NH--C(O)--(C.sub.1 -C.sub.6 -alkyl) or .dbd.NOH; or

a stereoisomeric form thereof, or a pharmaceutically acceptable salt thereof.

2.The compound according to claim 1 wherein R.sup.1 and R.sup.2 independently are H or C.sub.1 -C.sub.6 -alkyl.

3. The compound according to claim 2 of formula (II) ##STR8##

or a stereoisomeric form thereof, or a pharmaceutically acceptable salt thereof.

4. The compound of formula (II) according to claim 3 having .sup.1 H-NMR spectrum peaks at about 3.25. 3.34, 3.39, 3.45, 3.62, 3.69, 4.62, 6.75, 6.75, 7.25, 7.26, 7.28, 7.30, 7.38, 7.45, 7.62 ppm and .sup.13 C-NMR spectrum peaks at about 61.37, 70.47, 73.43, 78.4 (broad), 78.91, 81.29, 107,91, 108.19, 115.15, 115.27, 115.83, 117.58, 118.06, 118.72, 119.16, 124.95, 125.99, 126.37, 129.9 (broad), 130.13, 134.57, 135.66, 152.27, 152.57, 154.50, 154.76 ppm.

5. The compound according to claim 2 of formula (III) ##STR9##

having .sup.1 H-NMR spectrum peaks at about 6.69, 7.22, 7.24, 7.31 7.46 ppm and .sup.13 C-NMR spectrum peaks at about 109.20, 117.5, 119.55, 119.55, 121.3, 127.52, 130.63, 137.60, 154.3, 157.0 ppm, or a pharmaceutically acceptable salt thereof.

6. A process for the preparation of the compound of formula (I) as set forth in claim 1 comprising the steps of

a) culturing the ***microorganism*** ST 003360 (DSM 14093) or a ***variant*** and/or mutants of ST 003360 (DSM 14093) in a culture medium, and isolating and purifying the compound of the formula (II), or culturing the ***microorganism*** ST 004112 (DSM 14524 or a ***variant*** and/or mutants of ST 004112 (DSM 14524) in a culture medium, and isolating and purifying the compound of the formula (III),

b) converting the compound of formula (II) or the compound of formula (III) into the compound of formula (I), and

c) optionally converting the compound of formula (I) into a pharmaceutically acceptable salt.

7. The compound of formula (I) produced by the process of claim 6.

8. A process for the preparation of the compound of formula (II) according to claim 3 comprising the steps of

a) culturing the ***microorganism*** ST 003360 (DSM 14093 or a ***variant*** and/or ***mutant*** of ST 003360 (DSM 14093),

b) isolating and purifying the compound of formula (II), and

c) optionally converting the compound of formula (II) into a chemical equivalent or a pharmaceutically acceptable salt.

9. The compound of formula (II) produced by the process of claim 8.

10. A process for the preparation of the compound of formula (III) according to claim 5 comprising the steps of

a) culturing the ***microorganism*** ST 004112 (DSM 14524 or a ***variant*** and/or ***mutant*** of ST 004112 (DSM 14524),

b) isolating and purifying the compound of formula (III), and

c) optionally converting the compound of formula (III) in a chemical equivalent or a pharmaceutically acceptable salt.

DESCRIPTION

Instead of the strain Drechslera australiensis ST 003360, DSM 14093, or the strain ST 004112, DSM 14524, their respective mutants and/or variants can also be employed. A mutant is a microorganism in which one or more genes of the genome have been modified, the gene or the genes being functionally and hereditarily retained which are responsible for the capability of the organism to produce the inventive compound.

Such mutants can be produced in a manner well known to one skilled in the art by physical means, for example irradiation, such as using ultraviolet rays or X-rays, or chemical mutagens, such as, for example, ethyl methanesulfonate (EMS); 2-hydroxy-4-methoxy-benzophenone (MOB) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), or as described by Brock et al. in "Biology of Microorganisms", Prentice Hall, pages 238-247 (1994).

A variant is a phenotype of the microorganism. The microorganisms have the ability to adapt to their environment and therefore show marked physiological flexibility. In the phenotypic adaptation, cells of the microorganism are involved, the nature of the modification not being genetically conditioned and being reversible under modified conditions (H. Stolp, Microbial ecology: organisms, habitats, activities. Cambridge University Press, Cambridge, GB, page

180, 1988).

The screening for mutants and variants which produce the compounds according to the invention can be carried out by determination of the biological activity of the active compound accumulated in the culture broth, for example, by determination of the JNK-3- or hCK1.epsilon.-inhibiting action by methods well known to one skilled in the art, or by detection of such compounds, which are known as JNK-3- or hCK1.epsilon.-inhibitors, in the fermentation broth by, for example, HPLC or LC-MS methods that are well known to one skilled in the art.

The fermentation course and the formation of the compounds according to the invention can be monitored according to methods well known to one skilled in the art, such as, for example, by testing the biological activity in bioassays or by chromatographic methods such as thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC).

[this is exactly what is described on page 12 of our application]

US 10/608,466 filed June 27, 2003
L. VERTESY, et al
File: DEAV2002/0046US NP

EXHIBIT "B"

00495312616225

DSMZ
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

DSMZ Mascheroder Weg 1b D-38124 Braunschweig

Aventis Pharma Deutschland GmbH
A company of the sanofi-aventis group
Dr. Frank Sieber
Patent Department
Industriepark Höchst, Building K801
D-65926 Frankfurt am Main

U.S.S.N.: 10/676,715 filed 10/1/03
Hopmann et al; File: DEAV2002/0066US NP
EXHIBIT A

TELEFAX: 0049 69 357 175

Ihr Zeichen / Your ref.	Unser Zeichen / Our ref.	Tel.	Datum / Date
	P071 05/W	0531/2616- 254	2005-04-07
		vew@dsmz.de	

***Cryphonectria parasitica* DSM 14453**

Dear Dr. Sieber

The strain *Cryphonectria parasitica* DSM 14453 has been deposited at the DSMZ for the purposes of patenting according to *the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure*. The Treaty has been established by the World Intellectual Property Organization (WIPO), Geneva to meet the needs of patent applicants for biotechnological inventions. According to the Treaty certain culture collections are recognized by WIPO as International Depositary Authorities (IDAs). The DSMZ functions as patent depositary according to the Budapest Treaty since 1981 and holds more than 6000 patent strains. The main characteristics of an IDA as e.g. the DSMZ are (see Art.6, Status of International Depositary Authority):

....

(2) The depositary institution must, in its capacity of international depositary authority:

(iii) be impartial and objective;

(vii) comply, in respect of the deposited microorganisms, with the requirement of secrecy, as prescribed in the Regulations;

(viii) furnish samples of any deposited microorganism under the conditions and in conformity with the procedure prescribed in the Regulations.

Rule 9.2 of the Treaty specifies the demand for secrecy about biological material deposited according to the Budapest Treaty:

Rule 9.2 Secrecy

No international depositary authority shall give information to anyone whether a microorganism has been deposited with it under the Treaty. Furthermore, it shall not give any information to anyone concerning any microorganism deposited with it under the Treaty except to an authority, natural person or legal entity which is entitled to obtain a sample of the said microorganism under Rule 11 and subject to the same conditions as provided in that Rule.

DSMZ
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

As the DSMZ in its function as IDA follows the regulations of the Budapest Treaty, strains deposited according to the Treaty are handled in a separate department, will not be published and will never be listed in any publicly available list or in the DSMZ on-line catalogue. Consequently, nobody – except the depositor/patent applicant himself and the patent office involved - knows about the existence of a patent strain deposited according to the Budapest Treaty unless the patent application has been disclosed. Budapest Treaty deposits consequently will not appear in the public domain of the DSMZ.

Furnishing of samples of deposited biological material follows Rule 11 of the Treaty:

11.1 Furnishing of Samples to Interested Industrial Property Offices

Any international depositary authority shall furnish a sample of any deposited microorganism to the industrial property office of any Contracting State or of any intergovernmental industrial property organization, on the request of such office, provided that the request shall be accompanied by a declaration to the effect that:

....

11.2 Furnishing of Samples to or with the Authorization of the Depositor

Any international depositary authority shall furnish a sample of any deposited microorganism:

(i) to the depositor, on his request;

(ii) to any authority, natural person or legal entity (hereinafter referred to as "the authorized party"), on the request of such party, provided that the request is accompanied by a declaration of the depositor authorizing the requested furnishing of a sample.

11.3 Furnishing of Samples to Parties Legally Entitled

(a) Any international depositary authority shall furnish a sample of any deposited microorganism to any authority, natural person or legal entity (hereinafter referred to as "the certified party"), on the request of such party, provided that the request is made on a form whose contents are fixed by the Assembly and that on the said form the industrial property office certifies:

(i) that an application referring to the deposit of that microorganism has been filed with that office for the grant of a patent and that the subject matter of that application involves the said microorganism or the use thereof;

(ii) that, except where the second phrase of (iii) applies, publication for the purposes of patent procedure has been effected by that office;

....

It is evident that third parties will request Budapest Treaty deposits only after a patent application has been disclosed or patent protection has been granted. Without reference to a patent/application their requests cannot be handled at the IDA.

Sincerely yours,

V. Weihs

Dr. Vera Weihs

DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH